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BRIEF REPORT

A new pedigree with thrombomodulin-associated coagulopathy in which delayed fibrinolysis is partially attenuated by co-inherited TAFI deficiency

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Abstract

Background: Thrombomodulin-associated coagulopathy (TM-AC) is a rare bleeding disorder in which a single reported p.Cys537* variant in the thrombomodulin gene *THBD* causes high plasma thrombomodulin (TM) levels. High TM levels attenuate thrombin generation and delay fibrinolysis.

Objectives: To report the characteristics of pedigree with a novel *THBD* variant causing TM-AC, and co-inherited deficiency of thrombin-activatable fibrinolysis inhibitor (TAFI).

Patients/methods: Identification of pathogenic variants in hemostasis genes by next-generation sequencing and case recall for deep phenotyping.

Results: Pedigree members with a previously reported *THBD* variant predicting p.Pro496Argfs*10 and chain truncation in TM transmembrane domain had abnormal bleeding and greatly increased plasma TM levels. Affected cases had attenuated thrombin generation and delayed fibrinolysis similar to previous reported TM_AC cases with *THBD* p.Cys537*. Coincidentally, some pedigree members also harbored a stop-gain variant in *CPB2* encoding TAFI. This reduced plasma TAFI levels but was asymptomatic. Pedigree members with TM-AC caused by the p.Pro496Argfs*10 *THBD* variant and also TAFI deficiency had a partially attenuated delay in fibrinolysis, but no change in the defective thrombin generation.

Conclusions: These data extend the reported genetic repertoire of TM-AC and establish a common molecular pathogenesis arising from high plasma levels of TM extra-cellular domain. The data further confirm that the delay in fibrinolysis associated with TM-AC is directly linked to increased TAFI activation. The combination of the

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rare variants in the pedigree members provides a unique genetic model to develop understanding of the thrombin-TM system and its regulation of TAFI.

KEYWORDS
bleeding, fibrinolysis, genomics, TAFI (carboxypeptidase B2 [*CPB2*]/procarboxypeptidase U [proCPU]), thrombomodulin

1 | INTRODUCTION

The transmembrane protein thrombomodulin (TM) critically regulates blood coagulation by localizing thrombin to the vascular endothelial surface enabling the activation of several key substrates. The targets of the TM-thrombin complex include protein C, which after conversion to activated protein C (APC) limits further thrombin generation by inactivating coagulation factors Va and VIIIa.[1] TM also acts as a cofactor in thrombin-mediated activation of the procarboxypeptidase thrombin-activatable fibrinolysis inhibitor (TAFI) to activated TAFI (TAFIa). TAFIa attenuates the binding of tissue-type plasminogen activator (tPA) and plasminogen to fibrin by cleaving carboxyterminal lysines from partially degraded fibrin, thereby downregulating fibrinolysis.[2]

The physiological importance of TM is illustrated by the newly recognized autosomal dominant bleeding disorder thrombomodulin-associated coagulopathy (TM-AC), which to date has been associated with a single p.Cys537* variant in the thrombomodulin gene *THBD*.[3-6] This truncation variant results in excessive shedding of large quantities of the functionally active TM extracellular domain into plasma. This results in a significant bleeding diathesis because the high TM levels promote excessive generation of APC, which suppresses normal thrombin generation.[3-6] TM-AC is also associated with delayed fibrinolysis that can be corrected by inhibition of TAFIa, suggesting that the surplus TM in plasma stimulates thrombin-mediated TAFI activation.[3]

Here we report on a TM-AC pedigree with abnormal bleeding associated with a previously unreported *THBD* variant. We also describe how some pedigree members also harbor an independently inherited loss-of-function rare variant in *CPB2* resulting in reduction in TAFI levels and TAFIa generation and causing amelioration of the delayed fibrinolysis associated with TM-AC.

Essentials

- Thrombomodulin-associated coagulopathy (TM-AC) is linked to a single reported variant in *THBD*.
- The complex hemostatic defect comprises reduced thrombin generation and delayed fibrinolysis.
- We report a pedigree with a new *THBD* variant indicating a common molecular pathogenesis of TM-AC.
- Coinherited TAFI deficiency results in attenuated delayed fibrinolysis but not reduced thrombin generation.

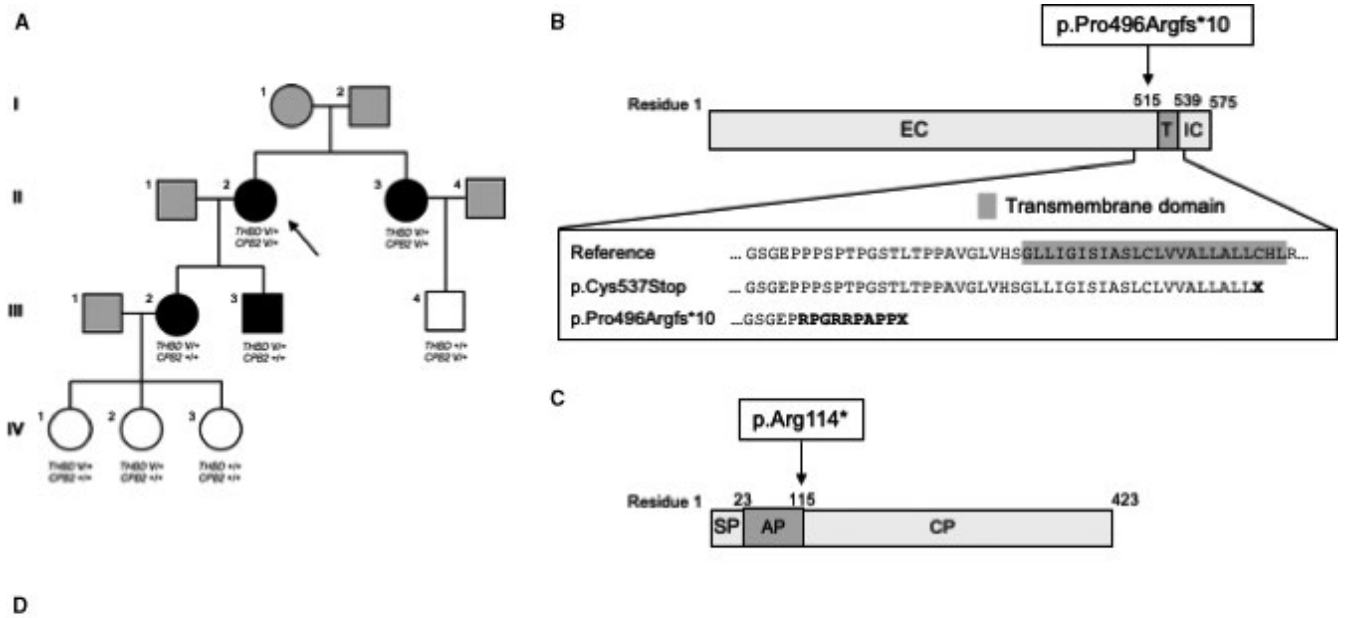
2 | METHODS

The study pedigree was identified in a systematic inspection of genotypes in the National Institute for Health Research BioResource–Rare Diseases, which included a collection of 1472 index cases with unexplained bleeding or platelet disorders enrolled between 2012 and 2016. Informed consent for enrolment and recall for extended phenotyping was in accordance with the Declaration of Helsinki (UK Research Ethics Committee approval 13/EE/0325). Procedures for collection of standardized phenotype terms, whole genome sequencing, and variant calling were as previously reported.[7] DNA sequencing for co-segregation analysis was performed using Sanger sequencing and the ThromboGenomics platform.[8] Thrombin generation and measurement of soluble TM, TAFI, and TAFIa concentrations were performed as described previously.[3,9-11] Thrombin generation was initiated with 1 pmol/L tissue factor in the presence of 4 μmol/L phospholipids. The clot lysis assays were performed using plasma diluted to 30% in 10 mmol/L Tris, 140 mmol/L NaCl, and 0.01% Tween-20 pH 7.4 and clot formation initiated with 10.6 mmol/L $CaCl_2$ and 0.1 U/mL thrombin (Sigma Aldrich) in the presence of 16 mmol/L phospholipids (Rossix) and 300 pmol/L tPA (Genentech).

3 | RESULTS/DISCUSSION

3.1 | Detection and annotation of the *THBD* and *CPB2* variants

Within the study collection, there was a single index case (II.2, Figure 1A) with a previously unreported high-impact *THBD* variant, similar to the variant in previously reported pedigrees with TM-AC.[3-6] This was a monoallelic single nucleotide deletion annotated as *THBD* c.1487delC, p.Pro496Argfs*10 relative to canonical transcript ENST00000377103.2. This predicted frameshift from codon 496 and a stop gain at codon 505 will result in loss of the final 11 residues of the TM extracellular domain, as well as the transmembrane domain and the intracellular domain (UniProtKB P07204; Figure 1B). Inspection of the coding regions of genes encoding known interactors of TM within the fibrinolysis pathway revealed that case II.2 also harbored a monoallelic variant in *CPB2*, encoding TAFI, annotated as c.340G>A; p.Arg114* relative to the canonical transcript



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	Age (years)	Bleeding symptoms	ISTH bleeding score	ETP (nM·min) [Control 1497]	Peak thrombin (nM) [Control 143]	Plasma TM (ng/ml) [2.9-7.6]	Plasma TAFI (U/L) [677-1309]	*THBD*	*CPB2*
II.2	64	PPH, dental, cutaneous	9	170	31	400	447	V/+	V/+
II.3	60	Dental*	4	NT	NT	364	704	V/+	V/+
III.2	42	PPH, dental	6	82	13	640	912	V/+	+/+
III.3	40	Dental, traumatic	6	83	12	514	1138	V/+	+/+
III.4	20	None	0	NT	NT	2.6	475	+/+	V/+
IV.1	14	None	0	NT	NT	598	NT	V/+	+/+
IV.2	11	None	0	NT	NT	698	NT	V/+	+/+
IV.3	8	None	0	NT	NT	2.46	NT	+/+	+/+

FIGURE 1 Genotype and laboratory characteristics of the thrombomodulin-associated coagulopathy cases. A, Pedigree showing the index case (→), indicating the genotype of the individuals for both the *THBD* and *CPB2* variants. The black symbols indicate cases with abnormal bleeding symptoms. The white symbols indicate pedigree members without bleeding symptoms, and the gray symbols indicate pedigree members unavailable for evaluation. V, variant allele; +, wild type allele. B, Schematic diagram of the mature thrombomodulin protein showing the position and amino acid sequence impact of the novel p.Pro496Argfs*10 in relation to the previously described variant associated with thrombomodulin-associated coagulopathy. EC, extracellular domain; T, transmembrane domain; IC, intracellular domain. C, Schematic diagram of the thrombin-activatable fibrinolysis inhibitor protein indicating the position of the novel p.Arg114* variant. SP, signal peptide; AP, activation peptide; CP carboxypeptidase domain. D, Clinical and laboratory characteristics of pedigree members showing *THBD* and *CPB2* genotypes. Bleeding symptoms were enumerated using the International Society on Thrombosis and Haemostasis (ISTH) bleeding assessment tool.[16] ETP, endogenous thrombin potential; TM, thrombomodulin; TAFI, thrombin-activatable fibrinolysis inhibitor; PPH, post-partum hemorrhage; V, variant allele; +, wild type allele; NT, not tested. *Indicates abnormal dental bleeding despite pro-hemostatic measures including antifibrinolytic and plasma treatment. Control ranges are shown in square brackets

ENST00000181383.10, which was absent in reference datasets.[7,12] This variant predicts premature truncation of the TAFI protein from residue 114, before the catalytic domain (residues 115-423),[2] thereby preventing functional TAFI expression from this allele (Figure 1C). The *THBD* variant p.Pro496Argfs*10 was identified in five further pedigree members (II.3, III.2, III.3, IV.1, and IV.2; Figure 1A). Only case II.3 also harbored *CPB2* p.Arg114*. A single pedigree member (III.4) harbored *CPB2* p.Arg114* but not *THBD* p.Pro496Argfs*10 (Figure 1A).

3.2 | Characteristics of the TM-AC cases

The adult cases with *THBD* p.Pro496Argfs*10 (II.2, II.3, III.2, and III.3) all reported bleeding (median International Society on Thrombosis and Haemostasis [ISTH] bleeding score 6 versus 0 in the unaffected adult pedigree member, Figure 1D), predominantly after dental procedures and trauma similar to previously reported TM-AC pedigrees,[3-6] but also after childbirth. Abnormal bleeding was not reported for the two cases in generation IV who were all aged 14 years or younger at enrolment and who had not undergone invasive dental or surgical procedures. Coinheritance of *CPB2* p.Arg114* (cases II.2 and II.3) had no discernible effect on the frequency or severity of bleeding. Plasma coagulation times, clotting factor levels, and platelet function testing in the *THBD* p.Pro496Argfs*10 cases were normal (data not shown). Consistent with previous reports of TM-AC, plasma TM levels were increased by at least two orders of magnitude in all pedigree members with *THBD* p.Pro496Argfs*10 (Figure 1D). Plasma TAFI levels were almost two-fold lower in the

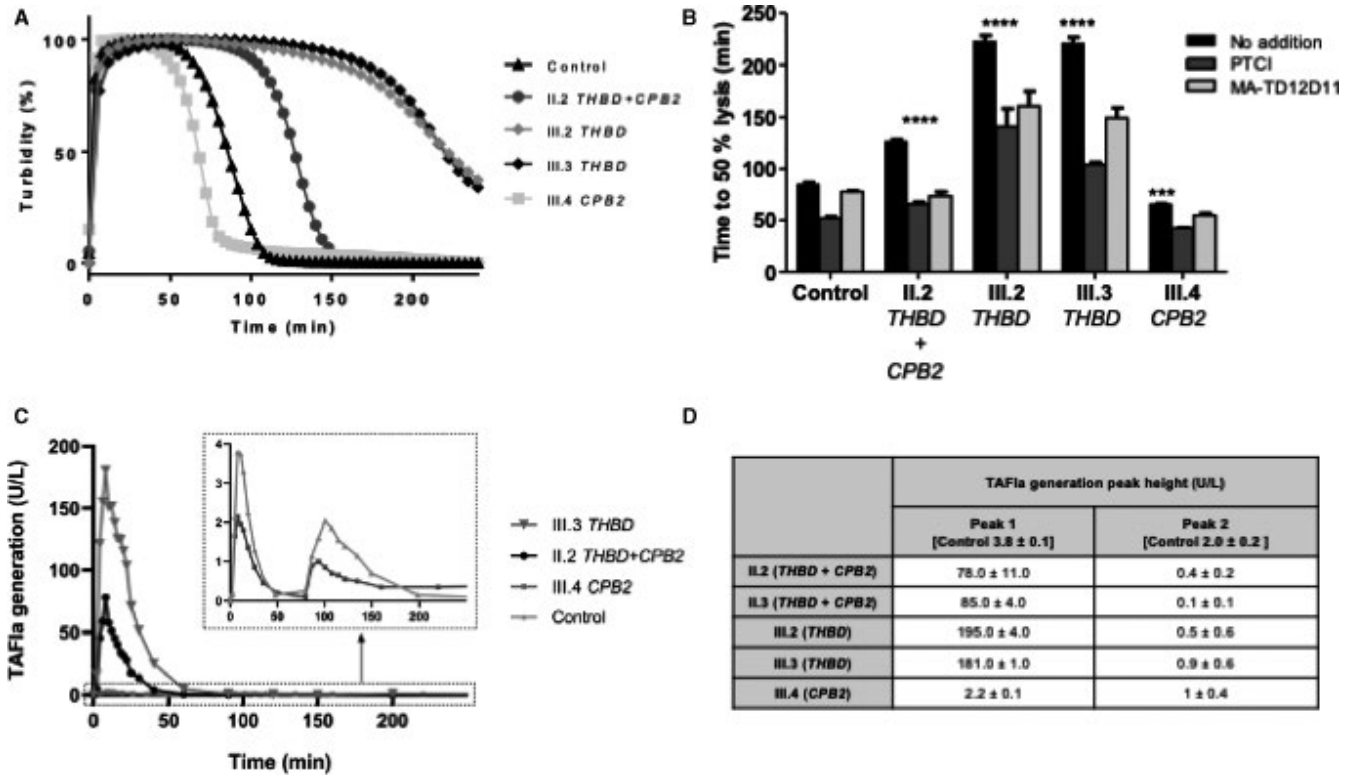
three cases harboring *CPB2* p.Arg114* compared to cases without this genotype (mean ± standard error of the mean [SEM] 542 ± 81 versus 1025 ± 113 U/L, Figure 1D), consistent with absent expression of the *CPB2* allele harboring the p.Arg114* variant.

To investigate potential interactions between the *THBD* and *CPB2* genotypes, we compared thrombin generation in plasma from adult pedigree members and control plasma (National Institute for Biological Standards and Control standard plasma) as previously reported.[3] The TM-AC cases (II.2, III.2, and III.3) demonstrated a reduction in endogenous thrombin potential and reduced peak thrombin concentration (Figure 1D). The differences in thrombin generation between cases and controls were smaller following initiation with 5 pmol/L tissue factor but the overall trend was the same (data not shown). These data with *THBD* p.Pro496Argfs*10 echo those of the previous descriptions of TM-AC associated with the p.Cys537* variant and are consistent with increased generation of APC and excessive suppression of thrombin generation.[3-6] The presence of the additional *CPB2* p.Arg114* variant in the TM-AC case II.2 had no discernible effect on thrombin generation.

3.3 | The *CPB2* p.Arg114* variant downregulates fibrinolysis

The effect of the *THBD* and *CPB2* variants on tPA-mediated fibrinolysis was analyzed by monitoring the turbidity of plasma samples after clot formation with 0.1 U/mL thrombin and calcium. In vitro plasma clot lysis was significantly delayed in samples from TM-AC cases III.2 and III.3 harboring the *THBD* variant alone (mean ± SEM time to 50% lysis [CLT] 223 ± 5.2 and 221 ± 5.9 minutes respectively versus 85 ± 1.9 minutes in control; $P < .0001$; Figure 2A, B), similar to previously reported cases with TM-AC.[3] In the TM-AC case II.2, who also harbors the *CPB2* p.Arg114* variant, fibrinolysis was delayed compared to control plasma, but to a lesser extent than the TM-AC cases without *CPB2* p.Arg114* (CLT 127 ± 1.6 minutes, $P < .0001$). Clot lysis was enhanced in case III.4 who had the *CPB2* p.Arg114* variant but did not carry the *THBD* mutation (CLT 66 ± 0.4 versus 85 ± 1.9 minutes in control, $P < .001$; Figure 2A, B).

To explore whether the modulatory effect of CPB2 p.Arg114* on fibrinolysis was a consequence of a reduction in the TAFI level, TAFIa



	TAFIa generation peak height (U/L)	
	Peak 1 [Control 3.8 ± 0.1]	Peak 2 [Control 2.0 ± 0.2]
II.2 (*THBD* + *CPB2*)	78.0 ± 11.0	0.4 ± 0.2
II.3 (*THBD* + *CPB2*)	85.0 ± 4.0	0.1 ± 0.1
III.2 (*THBD*)	195.0 ± 4.0	0.5 ± 0.6
III.3 (*THBD*)	181.0 ± 1.0	0.9 ± 0.6
III.4 (*CPB2*)	2.2 ± 0.1	1 ± 0.4

FIGURE 2 Delayed fibrinolysis in thrombomodulin-associated coagulopathy. A, Representative turbidity curves showing clot lysis in platelet-free plasma from controls or thrombomodulin-associated coagulopathy (TM-AC) cases. B, 50% lysis times were calculated from triplicate plasma samples using Shiny App for calculating clot lysis times.[17] Experiments were performed with and without 25 μg/mL potato tuber carboxypeptidase inhibitor (PTCI, Sigma Aldrich) or 65 μg/mL MA-T12D11.[11] Data shown represent the mean ± standard error of the mean of the turbidity measurements. ***$P < .001$ ****$P < .0001$ case versus control in plasma without thrombin-activatable fibrinolysis inhibitor (TAFI) inhibitors. Statistical significance was determined by one-way analysis of variance with Bonferroni's post hoc test. C, Representative profiles of biphasic activated TAFI (TAFIa) generation during in vitro clot lysis from controls or TM-AC cases. Clot lysis was performed as in (A) and simultaneously a second identical experiment was performed where at defined time points samples were collected and aprotinin (130 μg/mL) and trifluoroacetate salt (PPACK; 5 μmol/L) were added to stop TAFIa generation, after which the samples were placed on ice. Peak 1 (P1) and peak 2 (P2) correspond to thrombin-thrombomodulin-mediated and plasmin-mediated TAFIa generation respectively. D, TAFIa activity levels for P1 and P2 of TAFI generation during in vitro clot lysis for all adult pedigree members. Data represents mean ± standard deviation (n = 6)

concentration was measured during in vitro clot lysis. This model enables resolution of two peaks of TAFIa formation, generated first by TM/thrombin (P1) and subsequently by plasmin (P2; Figure 2C). In the TM-AC cases III.2 and III.3 who had the *THBD* variant alone, P1 was dramatically elevated almost 50-fold over controls. In pedigree members II.2 and II.3 that harbor both the *THBD* and *CPB2* p.Arg114* there was approximately a 50% reduction in P1 in the TAFIa generation curves compared to those members of the pedigree with *THBD* only (Figure 2C, D). P2 was diminished in all TM-AC cases, reflecting consumption of plasma TAFI in the first peak by excessive TM/thrombin-dependent activation. Both phases of TAFIa generation were significantly reduced in case III.4 with the *CPB2* p.Arg114* variant alone compared to the control, consistent with reduced plasma TAFI levels (Figure 2C, D). Pharmacological inhibition of TAFIa activity with potato tuber carboxypeptidase inhibitor (PTCI) or direct inhibition of thrombin-thrombomodulin mediated TAFI activation with the specific antibody MA-T12D11 partially corrected the delayed fibrinolysis in the TM-AC cases III.2 and III.3 with the *THBD* variant (Figure 2B). The concentrations of inhibitors included here had previously been used to overcome TAFIa activity in plasma.[3,13,14] However, in this study the exceptionally high concentrations of TM in the plasma of the case studies precluded the complete correction of clot lysis time. Higher concentrations of inhibitor were able to reduce levels further (data not shown). In TM-AC case II.2, who also harbors *CPB2* p.Arg114*, the same concentrations of inhibitor permitted more complete correction of the fibrinolytic abnormalities, with clot lysis times similar to those of control plasma (Figure 2B). These data are the first to describe a genetic deficiency of TAFI and emphasize the key role of TAFI in attenuating fibrinolysis in TM-AC.

4 | CONCLUSION

The pedigree described herein harbors a variant in *THBD* that marks only the second worldwide reported genetic variant to result in the rare bleeding disorder TM-AC. The variant identified, *THBD* p.Pro496Argfs*10, predicts protein chain truncation close to the transmembrane domain, thereby promoting excessive shedding of the TM extracellular domain. The marked elevation in plasma TM attenuates thrombin generation and delays fibrinolysis. This is a similar consequence to the *THBD* p.Cys537* variant associated with all previously described cases of TM-AC.[3-6] The reported results suggest a common pathogenic mechanism in both *THBD* variants in which the chain truncation promotes shedding of a functionally active TM extracellular domain into plasma.[15]

Remarkably, some pedigree members also harbor a pathogenic variant in *CPB2* predicting p.Arg114* in TAFI, resulting in partial deficiency of plasma TAFI levels. To our knowledge this is the first known case of a genetic deficiency in TAFI to be described in humans. We show that TAFI deficiency is clinically asymptomatic, but that the reduction of procarboxypeptidase activity in plasma accelerates fibrinolysis in vitro. Coinheritance of the *CPB2* p.Arg114* with *THBD* p.Pro496Argfs*10 partially ameliorates the delayed fibrinolytic profile associated with TM-AC, clearly demonstrating a crucial role for TAFI in this laboratory feature of TM-AC. The effect of this variant was similar to pharmacological inhibition of TAFIa in members of the pedigree with TM-AC. Analysis of this pedigree, in which members have highly impactful variants affecting two interacting coagulation pathway genes, enhances our understanding of ultra-rare human hemostatic disorders. The different combinations of the variants in the pedigree family members is a unique platform to allow insights into the regulation of the TM/thrombin system and TAFI activation that is highly relevant to a broad range of hemostatic disorders and therapies. The asymptomatic nature of genetic depletion of human TAFI underscores the potential to exploit inhibition of TAFI pharmacologically without bleeding complications.

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CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

S. K. Westbury analyzed sequencing and laboratory data and cowrote the manuscript; C. S. Whyte, J. C. Mertens, K. Claesen, and E. Leishman designed and performed experiments; J. Stephens performed DNA sequencing; E. Turro was chief analyst for the BioResource; K. Downes oversaw the genetic analysis in the Thrombogenomics program; A.-L. Latif enrolled study cases and provided phenotype descriptions; N. J. Mutch and D. Hendriks designed experiments and oversaw laboratory work; R. C. Tait enrolled study cases, provided phenotype descriptions, and oversaw the study; A. D. Mumford oversaw the study and cowrote the manuscript.

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